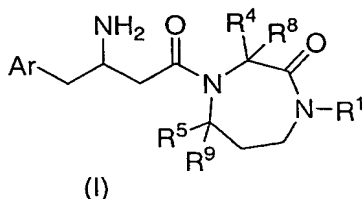


WHAT IS CLAIMED IS:

1. A compound of the formula I:



- 5 or a pharmaceutically acceptable salt thereof; wherein each n is independently 0, 1, or 2;
- Ar is phenyl substituted with one to five R^3 substituents;
- 10 R^1 is selected from the group consisting of
- hydrogen,
- C_{1-10} alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C_{1-6} alkoxy, carboxy, C_{1-6} alkyloxycarbonyl, and phenyl- C_{1-3} alkoxy, wherein alkoxy is unsubstituted or
- 15 substituted with one to five halogens,
- $(CH_2)_n$ -aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected from halogen, CN, hydroxy, R^2 , OR^2 , $NHSO_2R^2$, $NR^2SO_2R^2$, SO_2R^2 , CO_2H , and C_{1-6} alkyloxycarbonyl,
- $(CH_2)_n$ -heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three
- 20 substituents independently selected from hydroxy, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,
- $(CH_2)_n$ -heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with
- 25 one to five halogens,
- $(CH_2)_n$ - C_{3-6} cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C_{1-6} alkyl, and C_{1-6} alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one
- 30 to five halogens; and

wherein any methylene (CH₂) carbon atom in R¹ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens;

- 5 each R³ is independently selected from the group consisting of
hydrogen,
halogen,
cyano,
hydroxy,
10 C₁₋₆ alkyl, unsubstituted or substituted with one to five halogens,
C₁₋₆ alkoxy, unsubstituted or substituted with one to five halogens,
carboxy,
alkoxycarbonyl,
amino,
15 NHR²,
NR²R²,
NHSO₂R²,
NR²SO₂R²,
NHCOR²,
20 NR²COR²,
NHCO₂R²,
NR²CO₂R²,
SO₂R²,
SO₂NH₂,
25 SO₂NHR², and
SO₂NR²R²;

each R² is independently C₁₋₆ alkyl, unsubstituted or substituted with one to five substituents independently selected from halogen, CO₂H, and C₁₋₆ alkyloxy carbonyl;

- 30 R⁴ and R⁵ are independently selected from the group consisting of:
hydrogen,
cyano,
carboxy,

C₁₋₆ alkyloxycarbonyl,

C₁₋₁₀ alkyl, unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkoxy, carboxy,

C₁₋₆ alkyloxycarbonyl, and phenyl-C₁₋₃ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,

(CH₂)_n-aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_nCONR⁶R⁷, wherein R⁶ and R⁷ are independently selected from the group consisting of hydrogen, tetrazolyl, thiazolyl, (CH₂)_n-phenyl, (CH₂)_n-C₃₋₆ cycloalkyl, and C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five halogens and wherein phenyl and cycloalkyl are unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens;

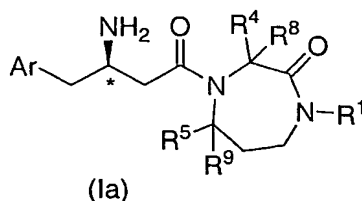
or wherein R⁶ and R⁷ together with the nitrogen atom to which they are attached form a heterocyclic ring selected from azetidine, pyrrolidine, piperidine, piperazine, and morpholine; and wherein said heterocyclic ring is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and wherein any methylene (CH₂) carbon atom in R⁴ or R⁵ is unsubstituted or

substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens; and

R⁸ and R⁹ are each independently hydrogen or C₁₋₆ alkyl.

5

2. The compound of Claim 1 of the formula Ia:



wherein the carbon atom marked with an * has the *R* configuration and Ar, R¹, R⁴, R⁵, R⁸, and R⁹ are as defined in Claim 1.

10

3. The compound of Claim 1 wherein R³ is selected from the group consisting of

hydrogen,

halogen,

15

cyano,

hydroxy,

C₁₋₆ alkyl, unsubstituted or substituted with one to five halogens, and

C₁₋₆ alkoxy, unsubstituted or substituted with one to five halogens.

20

4. The compound of Claim 3 wherein R³ is selected from the group consisting of hydrogen, fluoro, chloro, bromo, trifluoromethyl, and methyl.

5. The compound of Claim 4 wherein R³ is hydrogen, chloro, or fluoro.

25

6. The compound of Claim 1 wherein R¹ is selected from the group consisting of:

hydrogen,

C₁₋₆ alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkoxy, carboxy, C₁₋₆

alkyloxycarbonyl, and phenyl-C₁₋₃ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,
(CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens; and
wherein any methylene (CH₂) carbon atom in R¹ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens.

7. The compound of Claim 6 wherein R¹ is selected from the group consisting of

hydrogen,
C₁₋₄ alkyl,
2,2,2-trifluoroethyl,
methoxycarbonylmethyl,
carboxymethyl,
hydroxyethyl,
benzyloxymethyl,
benzyloxyethyl, and
cyclopropyl.

8. The compound of Claim 7 wherein R¹ is selected from the group consisting of hydrogen, methyl, *tert*-butyl, and cyclopropyl.

9. The compound of Claim 1 wherein R⁴ and R⁵ are independently selected from the group consisting of:

hydrogen,
C₁₋₁₀ alkyl, unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkoxy, carboxy, C₁₋₆ alkyloxycarbonyl, and phenyl-C₁₋₃ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,
(CH₂)_n-aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy,

wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-heterocyclyl, wherein heterocyclyl is unsubstituted or substituted with one to three substituents independently selected from oxo, hydroxy, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

wherein any methylene (CH₂) carbon atom in R⁴ or R⁵ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens.

10. The compound of Claim 9 wherein R⁴ and R⁵ are independently selected from the group consisting of:

hydrogen,

C₁₋₆ alkyl, unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkoxy, carboxy, C₁₋₆ alkyloxycarbonyl, and phenyl-C₁₋₃ alkoxy, wherein alkoxy is unsubstituted or substituted with one to five halogens,

(CH₂)_n-aryl, wherein aryl is unsubstituted or substituted with one to five substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to three substituents independently selected from hydroxy, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens,

(CH₂)_n-C₃₋₆ cycloalkyl, wherein cycloalkyl is unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₆ alkyl, and

C₁₋₆ alkoxy, wherein alkyl and alkoxy are unsubstituted or substituted with one to five halogens, and wherein any methylene (CH₂) carbon atom in R⁴ or R⁵ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl unsubstituted or substituted with one to five halogens.

11. The compound of Claim 10 wherein R⁴ and R⁵ are independently selected from the group consisting of:

hydrogen,
CH₃,
CH₂CH₃,
CH₂CH(CH₃)₂,
CH₂-cyclopropyl,
CH₂-cyclohexyl,
CH₂OCH₂Ph,
CH₂OH
CH₂Ph,
CH₂(3-OCF₃-Ph),
CH₂(4-OCF₃-Ph),
CH₂(3-CF₃,5-CF₃-Ph),
CH₂(2-CF₃-Ph),
CH₂(2-Cl-Ph),
CH₂(2-Me-Ph),
CH₂(2-Me,5-Me-Ph),
CH₂(2-Ph-Ph),
CH₂(2-F,5-F-Ph),
CH₂(2-F-Ph),
CH₂(2-F,3-F-Ph),
CH₂(2-pyridinyl),
CH₂(3-pyridinyl),
CH₂(4-pyridinyl),
CH₂(1-oxidopyridin-2-yl),
CH₂(1-oxidopyridin-3-yl),
CH₂(1H-pyrazol-1-yl),
CH₂(2-F,6-F-Ph), and

CH₂CF₃.

12. The compound of Claim 11 wherein R⁵ is hydrogen.

5 13. The compound of Claim 1 wherein R⁸ and R⁹ are independently selected from hydrogen and methyl.

14. The compound of Claim 13 wherein R⁸ and R⁹ are hydrogen.

10 15. The compound of Claim 1 wherein R¹ is selected from the group consisting of

hydrogen,
C₁₋₄ alkyl,
2,2,2-trifluoroethyl,
15 methoxycarbonylmethyl,
carboxymethyl,
hydroxyethyl,
benzyloxymethyl,
benzyloxyethyl, and
20 cyclopropyl;

R³ is hydrogen, chloro, or fluoro;

R⁴ is selected from the group consisting of:

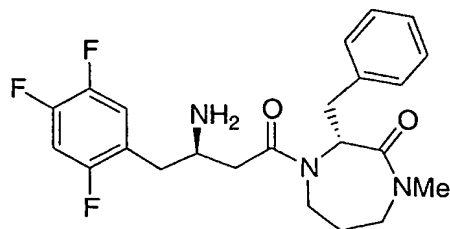
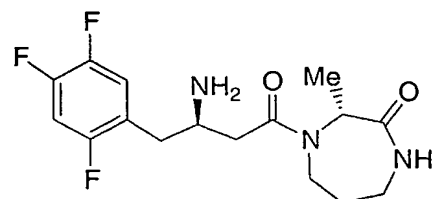
hydrogen,
CH₃,
25 CH₂CH₃,
CH₂CH(CH₃)₂,
CH₂-cyclopropyl,
CH₂-cyclohexyl,
CH₂OCH₂Ph,
30 CH₂OH
CH₂Ph,
CH₂(3-OCF₃-Ph),
CH₂(4-OCF₃-Ph), and
CH₂(3-CF₃,5-CF₃-Ph)
35 CH₂(2-CF₃-Ph),

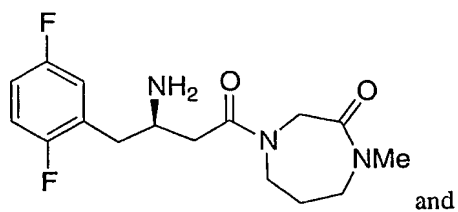
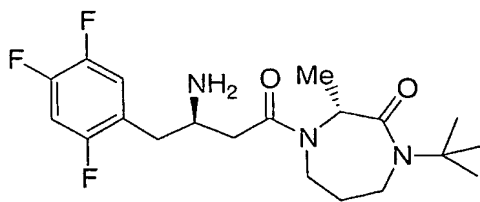
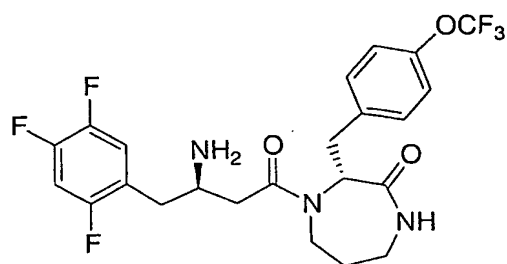
CH₂(2-Cl-Ph),
 CH₂(2-Me-Ph),
 CH₂(2-Me,5-Me-Ph),
 CH₂(2-Ph-Ph),
 5 CH₂(2-F,5-F-Ph),
 CH₂(2-F-Ph),
 CH₂(2-F,3-F-Ph),
 CH₂(2-pyridinyl),
 CH₂(3-pyridinyl),
 10 CH₂(4-pyridinyl),
 CH₂(1-oxidopyridin-2-yl),
 CH₂(1-oxidopyridin-3-yl),
 CH₂(1*H*-pyrazol-1-yl),
 CH₂(2-F,6-F-Ph), and
 15 CH₂CF₃; and

R⁸ and R⁹ are hydrogen.

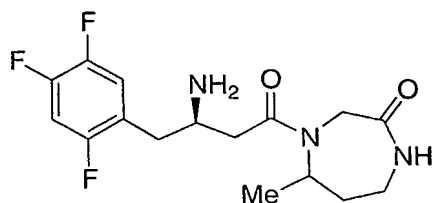
16. The compound of Claim 15 wherein R⁵ is hydrogen.

17. The compound of Claim 15 which is selected from the group consisting of



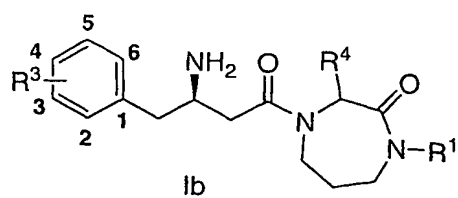


and



5 or a pharmaceutically acceptable salt thereof.

18. The compound of Claim 15 of structural formula Ib selected from the group consisting of



$\underline{R^3}$	$\underline{R^4}$	$\underline{R^1}$
2-F, 5-F	Me	H
2-F, 4-F, 5-F	CH ₂ -cPr	H
2-F, 4-F, 5-F	Me	Me
2-F, 5-F	Me	Et
2-F, 4-F, 5-F	Me	cPr
2-F, 5-F	Me	CH ₂ CO ₂ Me
2-F, 4-F, 5-F	Me	CH ₂ CH ₂ OH
2-F, 4-F, 5-F	Me	CH ₂ CH ₂ OCH ₂ C ₆ H ₅
2-F, 4-F, 5-F	Et	Me
2-F, 5-F	Et	Me
2-F, 4-F, 5-F	CH ₂ OH	Me
2-F	CH ₂ Ph	Me
3-F, 4-F	CH ₂ Ph	Me
2-F, 4-F, 5-F	CH ₂ OCH ₂ Ph	Me
2-F, 4-F, 5-F	Et	H
2-F, 4-F, 5-F	CH ₂ Ph	H
3-F, 4-F	CH ₂ Ph	H
2-F, 5-F	CH ₂ (4-OCF ₃ - Ph)	H
2-F, 4-F, 5-F	CH ₂ (3-OCF ₃ - Ph)	H
2-F, 4-F, 5-F	CH ₂ CH(CH ₃) ₂	Me

2-F, 4-F, 5-F	CH ₂ (3-CF ₃ ,5-CF ₃ -Ph)	H
2-F, 5-F	H	H
2-F, 4-F, 5-F	CH ₂ (2-CF ₃ -Ph)	H
2-F, 4-F, 5-F	CH ₂ (2-Cl-Ph)	H
2-F, 4-F, 5-F	CH ₂ (2-CH ₃ -Ph)	H
2-F, 4-F, 5-F	CH ₂ (2-CH ₃ ,5-CH ₃ -Ph)	H
2-F, 4-F, 5-F	Me	CHMe ₂
2-F, 4-F, 5-F	CH ₂ (2-Ph-Ph)	H
2-F, 4-F, 5-F	CH ₂ (2-F,5-F-Ph)	H
2-F, 4-F, 5-F	CH ₂ (2-F-Ph)	H
2-F, 4-F, 5-F	Me	CH ₂ CF ₃
2-F, 4-F, 5-F	CH ₂ (2-F,3-F-Ph)	H
2-F, 4-F, 5-F	CH ₂ (3-pyridyl)	H
2-F, 4-F, 5-F	CH ₂ (2-F-Ph)	CH ₂ CH ₂ CH ₃
2-F, 4-F, 5-F	CH ₂ (4-pyridyl)	H
2-F, 4-F, 5-F	CH ₂ (2-F-Ph)	Me
2-F, 4-F, 5-F	CH ₂ (2-pyridyl)	H
2-F, 4-F, 5-F	CH ₂ (2-F,6-F-Ph)	H
2-F, 4-F, 5-F	CH ₂ CF ₃	H

or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

20. A method for inhibiting dipeptidyl peptidase-IV enzyme activity in a mammal in need thereof which comprises the administration to the mammal of an effective amount of a compound of Claim 1.

5 21. A method for treating diabetes in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

10 22. A method for treating non-insulin dependent (Type 2) diabetes in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

15 23. A method for treating hyperglycemia in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

20 24. A method for treating obesity in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

25 25. A method for treating one or more lipid disorders selected from the group of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL and high LDL in a mammal in need thereof which comprises the administration to the mammal of a therapeutically effective amount of a compound of Claim 1.

30 26. A method for treating in a mammal in need thereof one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is

a component, wherein the method comprises the administration to the mammal a therapeutically effective amount of a compound of Claim 1.

27. The pharmaceutical composition of Claim 19 further comprising one or
5 more additional active ingredients selected from the group consisting of:
- (a) a second dipeptidyl peptidase IV inhibitor;
 - (b) an insulin sensitizer selected from the group consisting of a PPAR γ agonist, a PPAR α/γ dual agonist, a PPAR α agonist, a biguanide, and a protein tyrosine phosphatase-1B inhibitor;
 - 10 (c) an insulin or insulin mimetic;
 - (d) a sulfonylurea or other insulin secretagogue;
 - (e) an α -glucosidase inhibitor;
 - (f) a glucagon receptor antagonist;
 - (g) GLP-1, a GLP-1 mimetic, or a GLP-1 receptor agonist;
 - 15 (h) GIP, a GIP mimetic, or a GIP receptor agonist;
 - (i) PACAP, a PACAP mimetic, or a PACAP receptor agonist;
 - (j) a cholesterol lowering agent such as (i) HMG-CoA reductase inhibitor, (ii) sequestrant, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonist, (v) PPAR α/γ dual agonist, (vi) inhibitor of cholesterol absorption, (vii) acyl CoA:cholesterol
 - 20 acyltransferase inhibitor, and (viii) anti-oxidant;
 - (k) a PPAR δ agonist;
 - (l) an antiobesity compound;
 - (m) an ileal bile acid transporter inhibitor;
 - (n) an anti-inflammatory agent; and
 - 25 (o) an antihypertensive agent.

28. The pharmaceutical composition of Claim 27 wherein the PPAR α/γ dual agonist is KRP-297.

29. A method of treating diabetes in a mammal in need thereof comprising
30 administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with the PPAR α/γ dual agonist KRP-297.